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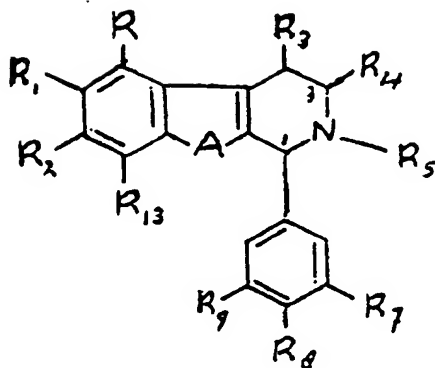
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(54) New beta-carbolines, their bio-isosteric benzofuran and benzothiophene analogues having
cytostatic properties.

(57) The invention relates to a group of new β -carbolines, their bio-isosteric benzofuran and benzothiophene
analogues, and to the preparation of these compounds.
The new compounds can be represented by the formula

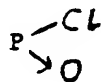
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(I)

wherein

- R, R₁ and R₂ are hydrogen, or R + R₁ or R₁ + R₂ form a saturated heterocyclic ring having 5 or 6 ring atoms, which comprise 1 or 2 oxygen atoms;
- R₃ is hydrogen, or hydroxy optionally derivatised with a sugar radical the 4,6-hydroxy groups of which are acetalised with an -ylidene group;
- R₄ is a group of the formula -C(R₁₁)₂-X-R₁₂, wherein the groups R₁₁ are hydrogen, or both groups R₁₁ together represent a double-bonded keto oxygen atom, X is oxygen or a group NR₁₄, wherein R₁₄ is hydrogen or alkyl having 1-4 C-atoms, and R₁₂ is hydrogen, alkyl having 1-4 C-atoms, alkanoyl having 1-4 C-atoms, the carbamoyl group or mono- or dialkylcarbamoyl group having 1-4 C-atoms per alkyl group;
- R₅ is hydrogen, alkanoyl or alkyl having 1-4 C-atoms, or R₄ + R₅ together form a group of the formula -C-(R₁₁)₂-X-Z, wherein R₁₁ and X have the above-mentioned meanings and Z is bound to the ring nitrogen atom and is a group >C=O, >C=S, >S=O or

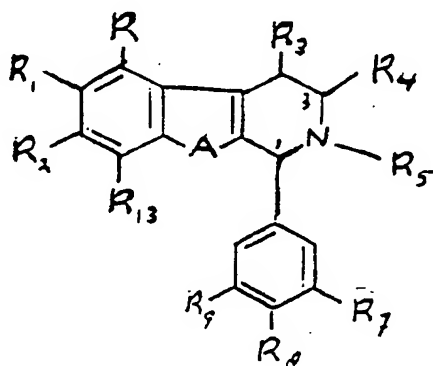


- R₇ and R₈ independently of each other are hydrogen or alkoxy having 1-4 C-atoms, trifluoromethyl or halogen;
 - R₈ is hydrogen, alkoxy or alkanoyloxy having 1-4 C-atoms, hydroxy, halogen, benzyloxy, or R₈ and R₉ together constitute a dioxyalkylidene bridge;
 - A is oxygen, sulphur or a group >NR₆, and
 - R₆ and R₁₃ independently of each other are hydrogen or methyl, or, when A is nitrogen, R₆ and R₁₃ together may form a ring having 5-7 C-atoms.
- The compounds have good cytostatic properties.

New β -carbolines, their bio-isosteric benzofuran and benzothiophene analogues having cytostatic properties.

The invention relates to a group of new β -carbolines, their bio-isosteric benzofuran and benzothiophene analogues, to the preparation thereof, and to pharmaceutical compositions which comprise at least one of the said compounds as an active substance.

It has been found that β -carbolines, their bio-isosteric benzofuran and benzothiophene analogues of the general formula



wherein

- R, R₁ and R₂ are hydrogen, or R + R₁ or R₁ + R₂ form a saturated heterocyclic ring having 5 or 6 ring atoms, which comprise 1 or 2 oxygen atoms;
- R₃ is hydrogen, or hydroxy optionally derivatised with a sugar radical the 4,6-hydroxy groups of which are acetalised with an -ylidene group;
- R₄ is a group of the formula -C(R₁₁)₂-X-R₁₂, wherein the groups R₁₁ are hydrogen, or both groups R₁₁ together represent a double-bonded keto oxygen atom, X is oxygen or a group NR₁₄, wherein R₁₄ is hydrogen or alkyl having 1-4 C-atoms, and R₁₂ is hydrogen, alkyl having 1-4 C-atoms, alkanoyl having 1-4 C-atoms, the carbamoyl group or mono- or dialkylcarbamoyl group having 1-4 C-atoms per alkyl group;
- R₅ is hydrogen, alkanoyl or alkyl having 1-4 C-atoms, or R₄ + R₅ together form a group of the formula -C(R₁₁)₂-X-Z, wherein R₁₁ and X have the above-mentioned meanings and Z is bound to the ring nitrogen atom and is a group >C=O , >C=S , >S-O or



- R₇ and R₈ independently of each other are hydrogen or alkoxy having 1-4 C-atoms, trifluoromethyl or halogen;
- R₈ is hydrogen, alkoxy or alkanoyloxy having 1-4 C-atoms, hydroxy, halogen, benzyloxy, or R₈ and R₉ together constitute a dioxyalkylidene bridge;
- A is oxygen, sulphur or a group >NR_6 , and
- R₆ and R₁₃ independently of each other are hydrogen or methyl, or, when A is nitrogen, R₆ and R₁₃ together may form a ring having 5-7 C-atoms, have very good cytostatic properties.

Examples of sugar radicals with which a hydroxyl group R₃ may be derivatised are glucoside and -ylidene glucosides, for example, benzyldene glucoside, thienyldene glucoside and ethyldene glucoside.

When in formula (I) one or more optically active carbon atoms are present, both the individual enantiomers and mixtures thereof belong to the invention.

Both the individual cis-isomers and trans-isomers and mixtures thereof belong to the invention.

The invention also relates to the acid addition salts and to prodrugs of the compounds of formula (I).

Prodrugs are to be understood to mean compounds which as such are inactive and which after administration into the body are converted into an active compound of formula (I).

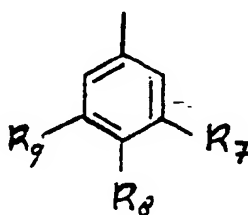
Suitable acids with which the compounds of formula (I) to be considered therefor can form pharmaceutically acceptable acid addition salts are, for example, hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids, for example, citric acid; fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methane sulphonic acid and naphthalene sulphonic acid.

The compounds according to the invention, their acid addition salts and prodrugs can be processed by means of standard techniques, to compositions, for example, pills, tablets, coated tablets, capsules, powders, injection liquids, and the like, while using auxiliary substances suitable for this purpose, for example, solid and liquid carrier materials.

The new compounds according to the invention can be obtained in a manner known for the synthesis of this type of compounds, for example, by means of Bischler-Napieralski (method A) or Pictet Spengler (method B) reactions.

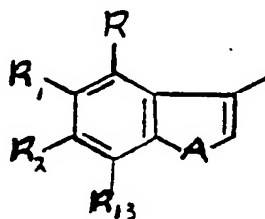
In the reaction schemes and tables hereinafter the following symbols have the indicated meaning:

- Z₁ is the group of formula



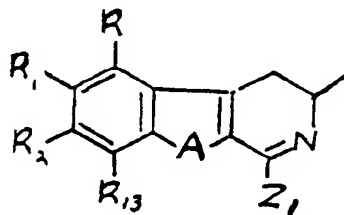
wherein R₇-R₉ have the above-mentioned meanings;

- Z₂ is the group of formula



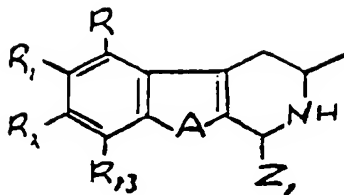
wherein R, R₁, R₂ and R₁₃ have the above-mentioned meanings, and A is oxygen, sulphur or a group NR_6 ;

- Z₃ is a group of the formula



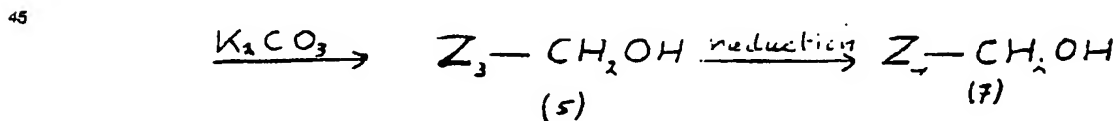
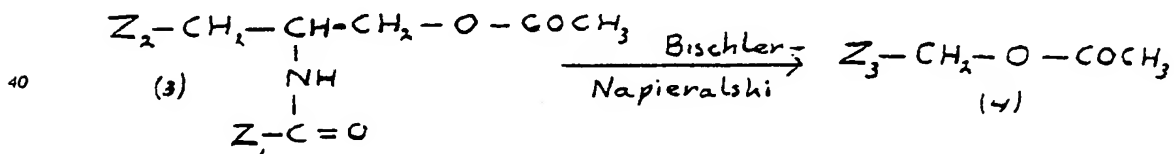
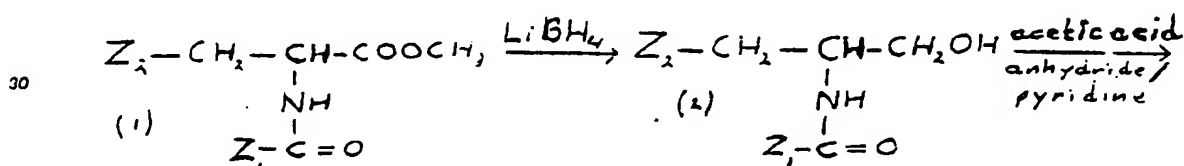
wherein R, R₁, R₂, R₁₃ and Z₁ have the above-mentioned meanings, and A is oxygen or sulphur;

- Z₄ is a group of the formula



- wherein R, R₁, R₂, R₁₃ and Z₁ have the above-mentioned meanings, and A is oxygen or sulphur, or a group >NR₅, wherein R₅ has the above mentioned meaning;
- Z₅ is the 3,4,5-trimethoxyphenyl group;
 - Z₆ is the 3,5-dimethoxyphenyl group
 - Z₇ is the 4-chlorophenyl group
 - Z₈ is the 3,4-dimethoxyphenyl group
 - Z₉ is the 4-hydroxy-3,5-dimethoxyphenyl group
 - Z₁₀ is the 3-methoxy-4,5-methylenedioxyphenyl group
 - Z₁₁ is the 3-methoxyphenyl group
 - Z₁₂ is the phenyl group
 - Z₁₃ is the 3-trifluoromethylphenyl group
 - Z₁₄ is the 3,5-dimethoxy-4-benzyloxyphenyl group.

Method A



Starting compounds (1) can be obtained in a manner known per se by reaction of a compound (1a) with (1b);

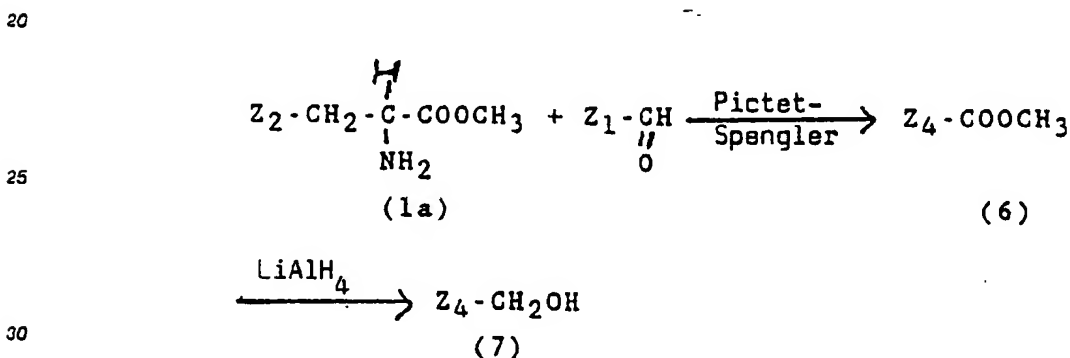


The compounds (1a) and (1b) are known compounds or can be obtained analogously to known compounds.

The reaction steps are carried out under conditions conventionally used for this type of reaction.

The so obtained compounds (5) can be converted in a manner known per se into compounds of formula I, wherein R₅ has the above-mentioned meanings a) by hydrogenating the double bond, for example, with AlCl₃ and LiAlH₄ (or by a catalytic reduction of a salt of (5)), or b) by reducing a quaternary derivative of compound (5) with NaBH₄ to obtain the trans-isomer.

Method B.



If desired, a substituent R₅ may be introduced in a manner known per se in the compounds (7) to be obtained in these manners.

The final products of formulae (5) and (7) respectively, to be obtained according to methods A and B may be converted in a manner known per se, for example, with phosgene, thionylchloride or phosphoroxo trichloride into compounds of formula I according to the invention, wherein R₄ + R₅ represent a group of the formula -C(R₁₁)₂-X-Z, wherein R₁₁, X and Z have the above-mentioned meanings.

The cytostatic activity of the compounds according to the invention was tested in two in vitro tests.

1. Human cell line cytotoxicity.

A number of representative compounds of the group according to the invention has been tested for cytotoxicity in at least five of the following human tumour cell lines: bladder T24, melanoma IGR37, breast MCF7, osteosarcoma A204, colon WIDR, HT29 and SW116 (P.P.Dendy and B.R. Hill, Human Tumour Drug, Sensitivity testing in vitro, Academic Press, 1983; H.B. Lamberts et al, Oncology 40, (1983), pp. 301-304; A.A. van der Huizen, Aziridiny cyclophosphazenes, synthesis, structure and cytostatic activity, thesis (1984), Groningen).

Procedure:

Cells are provided on 24-well cluster plates in a quantity of 10⁵ cells/ml of medium. After incubation at 37° C for 24 hours in an atmosphere of air with 5% of CO₂, a suspension of the compound to be tested in 0.5 of CMC/salt solution is added to a final concentration of 15µg/ml.

Adriamycin is used as a positive control compound. After incubation for 72 hours in the presence of the compound to be tested the cell layers are washed with a phosphate-buffered saline solution and the cells

are coloured with crystal violet. The cell growth inhibition is estimated with reference to the colour of cells and expressed as follows:

- 4 approximately 100% cell growth inhibition
- 3 approximately 75% cell growth inhibition
- 2 approximately 50% cell growth inhibition
- 1 approximately 25% cell growth inhibition
- 0 no cell growth inhibition.

2. Clonogenic test with human cell lines

A number of compounds according to the invention has been tested in the so-called clonogenic test (R. Ludwig et al, Cancer Chemother. Pharmacol. 12, (1984), pp. 135-141; W.I. Schaefer and K. Friend, Cancer Letters, 1, (1976), pp. 259-262; P.P. Dendy and B.T. Hill, Human Tumour Drug, Sensitivity testing in vitro, Academic Press, 1983). The following human cell lines are used: breast MCF7 and HTB26, colon WIDR and HTB38, lung HTB53, melanoma HTB66, and uterus HTB114.

Cisplatin, 5-fluorouracil, daunomycin, bleomycin and adriamycin are used as comparative substances.

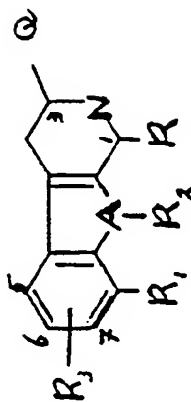
Procedure:

Each cell line is provided in a quantity of approximately 10^2 - 10^5 cells/dish and incubated in an atmosphere of air with 5% of CO₂ at 37°C. The compound to be investigated is added, during providing the cells or after a pre-incubation period of one night, as a solution or suspension in 0.5% of CMC/salt solution to a final concentration of 15µg/ml.

The duration of the treatment is approximately three times the cell division cycle. The cells are then fixed, coloured and evaluated for the presence of colonies. The colony formation is expressed in the number of colonies which is present on the treated dishes as a percentage of the number of colonies which is present on control dishes.

The activity of a number of compounds according to the invention is recorded in Tables A and B hereinafter as determined in test method 1.

TABLE A



comp. no.	R ₁	R ₂	R ₃	R	Q	A	3-D/L	1,3-cis/ trans	m.p. (°C)	cytotoxicity
1	H	H	H	Z5	CONH ₂	N	DL	cis	256	1-4
2	-(CH ₂) ₃ -	H	H	Z5	COOCH ₃	N	DL	cis	140	0-4
3	H	H	H	Z9	CONH ₂	N	DL	cis	>250	0-3
4	H	H	H	Z6	CONH ₂	N	D	cis	125	4-4
5	H	H	H	Z7	CONH ₂	N	D	cis	126	0-2
6	H	H	H	Z8	CONH ₂	N	D	cis	129	0-4
7	H	H	H	Z5	CH ₂ OH	N	DL	cis	190	0-4
8	H	H	H	Z5	CH ₂ OH	N	D	cis	212	4-4
9	-(CH ₂) ₃ -	H	H	Z5	CH ₂ OH	N	DL	cis	188	0-2
10	H	H	6,7-O(CH ₂) ₂ O	Z5	CH ₂ OH	N	DL	cis	135	0-4
11	H	H	H	Z6	CH ₂ OH	N	D	cis	125	4-4
12	H	CH ₃	H	Z5	CH ₂ OH	N	D	cis	>60	3-4
13	H	H	5,6-O(CH ₂) ₂ O-	Z5	CH ₂ OH	N	DL	cis	225	2-3

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comp. no.	R ₁	R ₂	R ₃	R	Q	A	3-D/L	1,3-cis/ trans	m.p. (°C)	cytotoxicity
14	H	H	H	Z5	CONH ₂	N	D	cis	147	4-4
15	H	H	H	Z5	CONH ₂	N	L	trans	126	0-4
16	H	H	H	Z5	CH ₂ OH	N	L	trans	102	0-4
17	H	-	H	Z5	CH ₂ OH	S	DL	cis	163	4-4
18	H	-	H	Z5	CH ₂ OH	S	DL	trans	148	4-4
19	H	-	H	Z5	CH ₂ OH	O	DL	cis	188	4-4
20	H	-	H	Z5	CH ₂ OH	O	DL	trans	151	3-4
21	H	H	H	Z6	CH ₂ OH	N	L	trans	65	2-4

Comp. no.	R1	R2	R3	R	A	R1
22	H	H	H	H	H	N
23	H	H	H	H	H	N
24	H	H	H	H	H	N
25	-(CH ₂) ₃ -	H	H	H	H	N
26	H	H	H	H	H	N
27	H	H	H	H	H	N
28	H	H	H	H	H	N
29	H	H	H	H	H	N
30	H	H	H	H	H	N
31	H	H	H	H	H	N
32	H	H	H	H	H	N
33	H	H	H	H	H	N
34	H	H	H	H	H	N
35	H	H	H	H	H	N

comp. no.	R ₁	R ₂	R ₃	R	A	X-Y	3-D/L	1-3 cis/trans	m.p. (°C)	cyto-tox.
36	H	H	H	Z ₅	N	O-C=O	L	trans	170	4-4
37	H	H	H	Z ₉	N	O-C=O	D	cis	159	4-4
38	H	H	H	Z ₉	N	O-C=O	D	trans	167	4-4
39	H	H	H	Z ₅	N	O-P→O ¹) Cl	D	cis	222	3-4
40	H	H	H	Z ₅	N	O-P→O ¹) Cl	D	cis	199	3-4
41	H	H	H	Z ₅	N	O-C=O	D	trans	183	0-2
42	H	H	H	Z ₅	N	NH-C=O	L	trans	145	4-4
43	H	H	H	Z ₁₀	N	O-C=O	L	trans	216	4-4
44	H	H	H	Z ₁₁	N	O-C=O	L	trans	208	4-4
45	H	H	H	Z ₆	N	O-C=O	L	trans	200	4-4
46	H	H	H	Z ₁₁	N	O-C=O	D	cis	207	4-4
47	H	CH ₃	H	Z ₅	N	O-C=O	D	cis	210	4-4
48	H	H	H	Z ₆	N	O-S→O ¹)	L	trans	170	4-4
49	H	H	H	Z ₆	N	O-S→O ¹)	L	trans	144	4-4
50	H	-	H	Z ₅	S	O-C=O	DL	trans	260	4-4

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comp. no.	R ₁	R ₂	R ₃	R	A	X-Y	3-D/L	1-3 cis/ trans	m.p. (°C)	cyto- tox.
51	H	-	H	Z ₅	S	O-C=O	DL	cis	298	4-4
52	H	H	H	Z ₁₂	N	O-C=O	L	trans	257	4-4
53	H	H	H	Z ₁₃	N	O-C=O	L	trans	>230	4-4
54	H	H	H	Z ₁₄	N	O-C=O	L	trans	106	4-4
55	H	H	H	Z ₉	N	O-C=O	L	trans	171	2-4
56	H	H	H	Z ₆	N	NH-C=O	L	trans	191	4-4
57	H	H	H	Z ₆	N	NH-C=S	L	trans	204	4-4
58	H	-	H	Z ₅	O	O-C=O	DL	cis	246	4-4
59	H	-	H	Z ₅	O	O-C=O	DL	trans	260	4-4
60	H	H	H	Z ₅	N	O-C=S	L	trans	249	4-4

1) pair of stereoisomers

EXAMPLE I

15 g Of (R)-1-(3,4,5-trimethoxyphenyl)-3-carbomethoxy- β -carboline were dissolved in 75 ml of dry tetrahydrofuran (THF). This solution was added dropwise to a suspension of 3.8 g of lithiumaluminium hydride in 50 ml of dry THF at a temperature below 10 °C. The solution was then stirred at room temperature for 2.5 hours. After cooling again to 5-10 °C 3.8 ml of water, 7.6 ml of 2N NaOH and 7.6 ml of water were added dropwise successively. After stirring at room temperature for 1 hour the precipitate was sucked off and the filtrate was evaporated. The residue was recrystallised from ethyl acetate. Yield 8 g of compound 8 of Table A (pure 1,3-cis) having a melting-point of 212 °C. $[\alpha]_D^{25} = 13.25$ (methanol).

Example II

0.7 ml Of triethylamine were added at 0 °C to a solution of 184 mg of 3-hydroxymethyl-1,2,3,4-tetrahydro-1-(3,4,5-trimethoxyphenyl)- β -carboline in 5 ml. of dichloromethane. 0.7 ml Of a 1M solution of phosgene in dichloromethane were added dropwise likewise at 0 °C. After stirring at 0 °C for 30 minutes ice water was added. The organic layer was separated and washed with 2N HCl and with water. The organic layer was dried with MgSO₄, filtered and evaporated to dryness. The resulting brown residue was treated with 50 ml of ether and the precipitate was filtered off. Yield 140 mg of compound 22 (Table B) as a pale brown solid Melting-point 163 °C.

EXAMPLE III

1 ml Of triethylamine was added to a solution of 840 mg of 3-hydroxymethyl-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro- β -carboline in 10 ml of dichloromethane. 0.2 ml Of thionylchloride were then added dropwise at 0 °C and the mixture was stirred at room temperature for 18 hours. 50 ml Of water were added and extraction was carried out twice with 75 ml of dichloromethane. The organic layer was washed with 50 ml of 2N HCl and with 50 ml of water. After drying with MgSO₄, filtering and evaporating to dryness the residue was separated by means of flash chromatography with 25% of ether/petroleum ether 60-80 as an eluent. In this manner two fractions were obtained.
 Fraction I: 280 mg of white solid; melting-point 235 °C. The proton in 3-position and the group S-O are trans with respect to each other (compound No. 23).
 Fraction II: 190 mg of light-brown substance; melting-point 213 °C. The proton in 3-position and the group S-O are cis with respect to each other (compound No. 24, Table B).

EXAMPLE IV

1 g Of 3-carbomethoxy-1,2,3,4-tetrahydro-1-(3,4,5-trimethoxyphenyl)- β -carboline was added to 25 ml of methanol (saturated with NH₃). The mixture was stirred at room temperature for 72 hours. The resulting suspension was filtered, which resulted in 230 mg of white solid. The filtrate was evaporated and the residue was treated with ether. After filtering the undissolved substance, another 520 mg of product were obtained. Yield 750 mg of amide (compound No. 1, Table A) having a melting-point of 256 °C.

Example V

To 1.92 g of 1-(3,4,5-trimethoxyphenyl)-3-hydroxymethyl-3,4-dihydro-pyrido[3,4-b]benzo[b]thiophene (obtained according to preparation b) for starting materials) in 25 ml of acetonitrile is added 1.1 g of benzyl bromide. The mixture is refluxed overnight and then evaporated in vacuo. After triturating the residue with ether, the white solid is dissolved in 25 ml of methanol and cooled to -70 °C; 0.5 g of sodium borohydride is added portionwise. After stirring for 1 hour at -70 °C, 10 ml of acetone is added.

The mixture is warmed to room temperature and stirred for 2 hours. After concentrating in vacuo the residue is brought in dichloromethane and washed with brine. The organic layer is dried over MgSO₄ and evaporated in vacuo. The resulting residue is dissolved in 50 ml of acetic acid and hydrogenated over palladium or charcoal. The catalyst is filtered off and the filtrate is evaporated in vacuo. The residue is washed with 5% of sodium bicarbonate and purified by flash chromatograph with 2% of methanol in

dichloromethane. By this method compound no. 18 of table A is obtained having a melting point of 148° C.

a) Preparation of a starting compound as used in Example I.

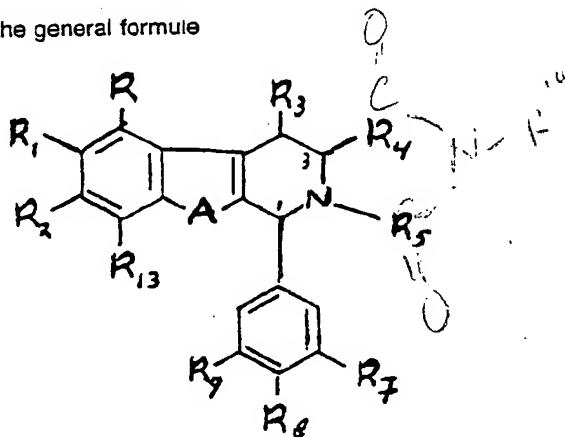
To a suspension of 4 g of L-tryptophan ethyl ester in 75 ml of toluene is added 3.5 g 3,5-dimethoxy benzaldehyde. The reaction mixture is refluxed for 8 hours and then 2 ml of trifluoroacetic acid is added. The mixture is refluxed again for 24 hours. After evaporation in vacuo, the residue is dissolved in 150 ml of methylene chloride and washed with sodium bicarbonate and water. The solution is dried over MgSO₄ and evaporated in vacuo. The so obtained mixture of cis and trans isomers is separated by flash chromatography with methylene chloride: methanol 99:1 as an eluent. By this method two fractions were obtained. Fraction 1: 2.5 g the cis isomer, melting point 155° C, and fraction 2: 2.2 g of the trans isomer, melting point 65° C. These isomers were reduced to the corresponding amino alcohols as described in example 1.

b) Preparation of a starting compound as used in Example V.

30 ml of phosphoroxo trichloride is added to a suspension of 10.08 g of ethyl- α -(3,4,5-trimethoxybenzoylamino- β -(benzofuran-3-yl)propionate in 60 ml of acetonitrile. The reaction mixture is refluxed for 16 hours and evaporated in vacuo. The residue is taken up in methylene chloride and washed with 5% of sodium bicarbonate solution until neutral. The solution is dried over MgSO₄ and evaporated in vacuo. The residue is taken up in methanol and stirred with 10 g of potassium carbonate for 1 hour. The reaction mixture is poured into water and extracted with methylene chloride. After drying over MgSO₄ and evaporation in vacuo 7.22 g of the compound (5) is obtained, wherein Z₁ in symbol Z₃ is the group Z₅, A is oxygen, and R = R₁ = R₂ = R₁₃ = H, i.e. 1-(3,4,5-trimethoxyphenyl-3-hydroxymethyl-3,4-dihydro-pyrido[3,4-b]benzo[b]furan, having a melting-point of 110° C.

Claims

1. Compounds of the general formule



wherein

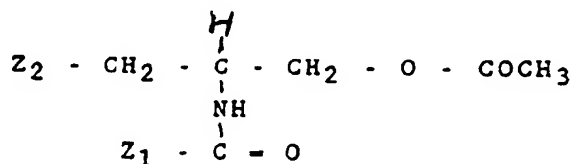
- R, R₁ and R₂ are hydrogen, or R + R₁ or R₁ + R₂ form a saturated heterocyclic ring having 5 or 6 ring atoms, which comprise 1 or 2 oxygen atoms;
- R₃ is hydrogen, or hydroxy optionally derivatised with a sugar radical the 4,6-hydroxy groups of which are acetalised with an -ylidene group;
- R₄ is a group of the formula -C(R₁₁)₂-X-R₁₂, wherein the groups R₁₁ are hydrogen, or both groups R₁₁ together represent a double-bonded keto oxygen atom, X is oxygen or a group NR₁₄, wherein R₁₄ is hydrogen or alkyl having 1-4 C-atoms, and R₁₂ is hydrogen, alkyl having 1-4 C-atoms, alkanoyl having 1-4 C-atoms, the carbamoyl group or mono- or dialkylcarbamoyl group having 1-4 C-atoms per alkyl group;
- R₅ is hydrogen, alkanoyl or alkyl having 1-4 C-atoms, or R₄ + R₅ together form a group of the formula -C(R₁₁)₂-X-Z, wherein R₁₁ and X have the above-mentioned meanings and Z is bound to the ring nitrogen atom and is a group >C=O, >C=S, >S-O or



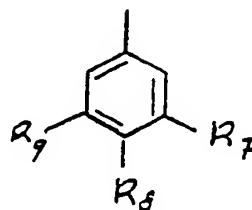
- R_7 and R_9 independently of each other are hydrogen or alkoxy having 1-4 C-atoms, trifluoromethyl or halogen;
- R_8 is hydrogen, alkoxy or alkanoyloxy having 1-4 C-atoms, hydroxy, halogen, benzyloxy, or R_8 and R_9 together constitute a dioxyalkylidene bridge;
- A is oxygen, sulphur or a group $> \text{NR}_6$, and
- R_6 and R_{13} independently of each other are hydrogen or methyl, or, when A is nitrogen, R_6 and R_{13} together may form a ring having 5-7 C-atoms,

and salts thereof with pharmaceutically acceptable acids.

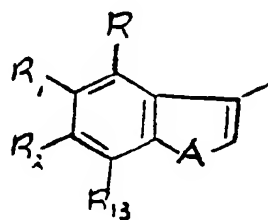
2. A method of preparing compounds as claimed in Claim 1, characterised in that a compound of the formula



wherein Z_1 is a group of the formula



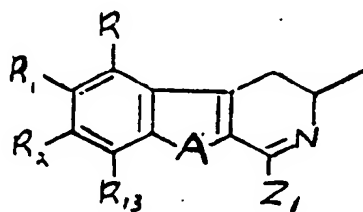
and Z_2 is a group of the formula



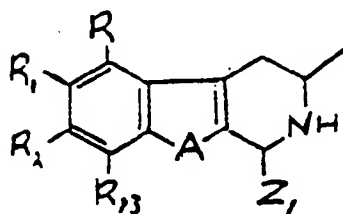
wherein the symbols have the meanings mentioned in Claim 1 on the understanding that A is oxygen or sulphur, is converted according to Bischler-Napieralski into a compound

$Z_3 - \text{CH}_2 - \text{O} - \text{COCH}_3$

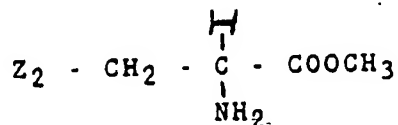
wherein Z_3 is a group of the formula



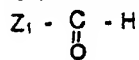
wherein the symbols have the above mentioned meanings, and the acetoxy group is converted in a manner known per se into the hydroxy group, and reducing group Z₃ to a group Z₄ of the formula



3. A method of preparing compounds as claimed in Claim 1, characterised in that a compound of the formula



is converted according to Pictet-Spengler with a compound of the formula



wherein Z₁ has the meaning mentioned in Claim 2, into a compound of the formula Z₄-COOCH₃, wherein Z₄ is the group mentioned in claim 2, wherein the symbols have the meanings mentioned in Claims 1 and 2, on the understanding that A in groups Z₂ and Z₄ is nitrogen, and the resulting compound is converted in a manner known per se into a compound of formula Z₄-CH₂OH

4. A method as claimed in Claim 2 or 3, characterised in that a substituent R₅ is introduced in a manner known per se.

5. Compositions having cytostatic properties, characterised in that they comprise at least one compound as claimed in Claim 1 as an active substance.

6. A method of preparing compositions as claimed Claim 5, characterised in that a compound as claimed in Claim 1 is brought into a form suitable for administration.

7. A method of treating tumours, characterised in that a compound as claimed in Claim 1 is used.



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Publication number: **0 357 122 A3**

12

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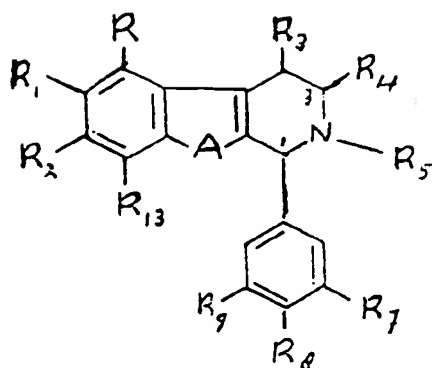
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54 **New beta-carbolines, their bio-isosteric benzofuran and benzothiophene analogues having cytostatic properties.**

57 The invention relates to a group of new β -carbolines, their bio-isosteric benzofuran and benzothiophene analogues, and to the preparation of these compounds.
The new compounds can be represented by the formula

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(I)

wherein

- R, R₁ and R₂ are hydrogen, or R + R₁ or R₁ + R₂ form a saturated heterocyclic ring having 5 or 6 ring atoms, which comprise 1 or 2 oxygen atoms;

- R₃ is hydrogen, or hydroxy optionally derivatised with a sugar radical the 4,6-hydroxy groups of which are acetalised with an -ylidene group;

- R₄ is a group of the formula -C(R₁₁)₂-X-R₁₂, wherein the groups R₁₁ are hydrogen, or both groups R₁₁ together represent a double-bonded keto oxygen atom, X is oxygen or a group NR₁₄, wherein R₁₄ is hydrogen or alkyl having 1-4 C-atoms, and R₁₂ is hydrogen, alkyl having 1-4 C-atoms, alkanoyl having 1-4 C-atoms, the carbamoyl group or mono- or dialkylcarbamoyl group having 1-4 C-atoms per alkyl group;

- R₅ is hydrogen, alkanoyl or alkyl having 1-4 C-atoms, or R₄ + R₅ together form a group of the formula -C(R₁₁)₂-X-Z, wherein R₁₁ and X have the above-mentioned meanings and Z is bound to the ring nitrogen atom and is a group



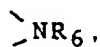
or



- R₇ and R₉ independently of each other are hydrogen or alkoxy having 1-4 C-atoms, trifluoromethyl or halogen;

- R₈ is hydrogen, alkoxy or alkanoyloxy having 1-4 C-atoms, hydroxy, halogen, benzyloxy, or R₈ and R₉ together constitute a dioxyalkylidene bridge;

- A is oxygen, sulphur or a group



and

- R₆ and R₁₃ independently of each other are hydrogen or methyl, or, when A is nitrogen, R₆ and R₁₃ together may form a ring having 5-7 C-atoms.

The compounds have good cytostatic properties.



European Patent
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EUROPEAN SEARCH REPORT

Application Number

EP 89 20 2089

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL.5)
X	US-A-4 336 260 (DOW)(22-06-1982) * Table 1 * ---	1	C 07 D 471/04 C 07 D 471/06
X	FR-A-1 310 972 (GEIGY)(22-10-1962) * Page 3, column 1, lines 15-33; column 2, lines 1-10 * ---	1	C 07 D 491/147 C 07 D 498/14 C 07 D 515/14 C 07 D 498/16 C 07 D 498/22
X	GB-A- 975 835 (GEIGY) * Claim 1 * ---	1	C 07 F 9/6584 C 07 D 495/04
X	FR-A-1 310 971 (GEIGY)(1962) * Claim 1 * ---	1	C 07 D 491/048 A 61 K 31/435 //
X	FR-A-1 310 970 (GEIGY)(1962) * Claim 1 * ---	1	(C 07 D 471/04 C 07 D 221:00 C 07 D 209:00) (C 07 D 471/06 C 07 D 221:00 C 07 D 209:00) -/-
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 25, 1982, pages 1081-1091, American Chemical Society, Columbus, Ohio, US; M. CAIN et al.: "Beta-carbolines: Synthesis and neurochemical and pharmacological actions on brain benzodiazepine receptors" * Pages 1081-1091, compound 59 * ---	1	TECHNICAL FIELDS SEARCHED (Int. CL.5) C 07 D 471/00 C 07 D 491/00 C 07 D 495/00 C 07 D 498/00 C 07 D 519/00 C 07 F 9/00 A 61 K 31/00
X	CHEMICAL ABSTRACTS, vol. 94, 1981, page 685, abstract no. 121371w, Columbus, Ohio, US; T. NAGASAKA et al.: "Diisopropylamine as a coexisting base for alkylation of amines", & YAKUGAKU ZASSHI 1980, 100(9), 962-6 * Abstract and 10th Collective Index, page 46400, column 1, lines 67-69 * --- -/-	1	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 22-07-1991	Examiner ALFARO I.
CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons *: member of the same patent family, corresponding document			

EPO FORM 1500 (04/91) (Page 1)



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EUROPEAN SEARCH REPORT

Page 2

Application Number

EP 89 20 2089

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X	CHEMICAL ABSTRACTS, vol. 81, 1974, page 462, abstract no. 91485y, Columbus, Ohio, US; F. HAMAGUCHI et al.: "Synthesis of 1,3-disubstituted-1,2,3,4-tetrahydro-beta-carboline derivatives, and studies on their stereoisomers", & YAKUGAKU ZASSHI 1974, 94(3), 351-8 * Abstract and 9th Collective Index, page 34028, column 1, lines 14,15; column 2, lines 74,75 * ---	1	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
X	CHEMICAL PHARMACEUTICAL BULLETIN, vol. 33, no. 8, 1985, pages 3237-3249, Tokyo, JP; A. ISHIDA et al: "A new method for the preparation of 3,4-dihydro- and 1,2,3,4-tetrahydro-beta-carbolines" * Page 3244 (3b); page 3245 (3h, 3k); page 3246 (5b) * --- -/-	1	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 22-07-1991	Examiner ALFARO I.
CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document		T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons --- A: member of the same patent family, corresponding document	



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EUROPEAN SEARCH REPORT

Page 3

Application Number

EP 89 20 2089

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	CHEMICAL ABSTRACTS, vol. 96, 1982, page 588, abstract no. 198750t, Columbus, Ohio, US; S. KUMAR et al.: "Stereochemical assignment of 3-(methoxycarbonyl)-1-substituted-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indoles by mass spectrometry", & INDIAN J. CHEM., SECT. B 1981, 20B(12), 1078-9 * Abstract and 11th Collective Index, page 59221, column 3, lines 48-52 *	1	
A	EP-A-0 251 361 (DUPHAR)(07-01-1988) * Claims 1,9 *	1,5	
A	WO-A-8 800 826 (HARBOR BRANCH OCEANOGRAPHIC INSTITUTION)(11-02-1988) * Claim 1 *	1,5	
P,X	EP-A-0 300 541 (DUPHAR) * Claim 1; page 8, compound 6 *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 22-07-1991	Examiner ALFARO I.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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